EXHIBIT "A"

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

James C. Powers

Serial No.: 10/671,360

Filed: September 25, 2003

Confirmation No.: 7114

Group Art Unit: 1654

Examiner: Christina Bradley

Docket No.: 820701-1015

For: Ketoamide Inhibitors in Chronic Nerve Disease

DECLARATION OF JAMES C. POWERS PURSUANT TO 37 C.F.R. §1.132

Commissioner for Patents
Alexandria, Virginia 22313-1450

Sir,

I, **James C. Powers**, hereby declare that:

Education and Experience

1. I am a co-inventor of the 10/671,360 application (hereinafter "the '360 application").

2. I graduated from Wayne State University with a Bachelor of Science in Chemistry (1959), and from Massachusetts Institute of Technology with a Ph.D. in Chemistry (1963). I have also had extensive postgraduate training, including a postdoctoral research fellowship as a Special NIH fellow at the University of Washington (1967-1970).

3. I am an inventor or co-inventor on 34 active patents and 4 patent applications currently pending, including U.S. Pat. No. 5,610,297 and 5,650,508 directed to the chemical compound Z-Leu-Abu-$(CH_2)_3$-4-morpholinyl (AK295).

4. Since graduating with my Ph.D., I have been involved in a variety of pursuits related to the field of enzyme catalysis and enzyme inhibition, specifically the development of synthetic inhibitors of proteolytic enzymes. In addition to the postgraduate training mentioned above, I have held many academic, clinical, and academic appointments at various institutions including the University of California Los Angeles (UCLA), and the University of Washington, and currently hold a tenured position at the Georgia Institute of Technology as a Regents Professor of Chemistry and Biochemistry. I have also spent sabbatical leaves at the University of Washington and at Parke Davis research (now Pfizer) in Ann Arbor, Michigan. I have held or currently hold memberships with several academic/scientific foundations and societies including the American Chemical Society, American Association for the Advancement of Science, and the American Society for Biochemistry and Molecular Biology. I have served on grant review committees for the National Institutes of Health and other granting organizations. I am a member or advisor to many institutional committees at the Georgia Institute of Technology. I served as an editor or an editorial board member for scientific journals including, Current Protein And Peptide Science, J. Enzyme Inhibition and Medicinal Chemistry, J. of Protein Chem., Biochemistry, and ISI Atlas of Science. I have also served as a reviewer for a number of other scientific journals, such as J. Am. Chem. Soc., Biochemistry, J. Med. Chem., Anal. Biochem., Protein Science, Science, J. Org. Chem., Bioorganic and Natural Products Chemistry, Bioorganic & Medicinal Chemistry Letters, Arch. Biochemistry and Biophysics, among others. I have consulted for numerous industrial companies including BioCryst, BASF Biotechnology Corp, Cortex, Vascular Therapeutics (Scientific Advisory Board), Osteoarthritis Sciences, Inc., Corvas International, Inc., Athens Research and Technology, Berlex Laboratories, Inc. (Scientific Advisory Board), Gentili (Pisa, Italy), Cetus, Prototec, Merck, Inc., Coulter Electronics and Immunology, and Greenhouse Management Corp. I have presented

over 100 seminars and invited lectures at national and international meetings, academic institutions, and industrial companies on synthetic protease inhibitors. I have published over 200 research and articles in scientific journals and 35 book chapters or review articles. I have been principle investigator on over 80 research grants, which have primarily been funded by the National Institutes of Health, but include a variety of other federal and industrial organizations. The total amount of funded research at Georgia Tech exceeds $10,000,000. My research focus is on proteolytic enzymes and the development of synthetic inhibitors for such proteases. Specifically, my research includes the development of both mechanism-based and transition-state inhibitors for proteases such as caspases and calpains and the therapeutic use of such inhibitors to treat conditions associated with calpain activity (e.g., conditions associated with neurodegeneration) and caspase activity (e.g., inflammation, cancer, Alzheimer's disease, *etc.*). I also teach several undergraduate and graduate courses at Georgia Institute of Technology and supervise doctoral candidates and post-doctoral fellows.

5. Through my education and research in enzyme mechanisms and the development of synthetic inhibitors, especially inhibitors of proteolytic enzymes of therapeutic importance, I have gained extensive experience in the field of proteases, their inhibitors, and the use of such inhibitors for the treatment of disease, including calpain inhibitors and their use for the treatment of various neurological conditions.

The Office Action and Presently Pending Claims

6. I have reviewed the Office Action mailed on August 23, 2006 and understand that the presently pending claims stand rejected under 35 U.S.C. §103(a), as allegedly unpatentable over Saatman *et al.* (Proc. Natl. Acad. Sci. USA, 93, 3428-3433 (1996)) (hereinafter, "Saatman") in view of Wang *et al.* (J. Neuropathology and

Experimental Neurology, 59, 599-606 (2000)) (hereinafter "Wang") and Schaecher *et al.* (Neurochemical Research, 26, 731-737 (2001))(hereinafter "Schaecher").

7. I have been involved in the drafting of the '360 application and prosecution of the presently pending claims. Presently pending claim 1 is directed to a method of treating axonal degeneration of the peripheral nervous system in a patient by administering to the patient an effective amount of a compound of the formula M^1-AA^2-AA^1-CO-NR_3R_4 (as defined in the '360 application), which includes the compound Z-Leu-Abu-$(CH_2)_3$-4-morpholinyl (AK295).

8. I understand that the Office Action takes the position that the combined teachings of Saatman, Wang, and Schaecher render the claimed methods of treating axonal degeneration of the peripheral nervous system obvious to one of skill in the art.

Discussion

9. With respect to the Saatman reference, this reference deals with major trauma to the head, which is part of the central nervous system. Head injured animals exhibit major motor and cognitive dysfunction following injury. They experience loss of many types of neurological cells in the brain following the injury. In my opinion and based on my experience with calpain inhibitors and AK295 specifically, the effectiveness of AK295 in reducing the severity of the effects of the injury in the brain doesn't predict that AK295 would be effective in treatment of axonal degeneration in peripheral tissue during peripheral neuropathy (PN). PN results from injury to axons due to treatment with neurotoxic agents or due to diseases such as diabetes. It develops more slowly than a single traumatic injury to the central nervous system (CNS, i.e., brain and spinal cord). PN also more selectively affects axons and not the many types of tissues and cells injured in a head trauma. The experiments reported by Saatman describe protection

against neuronal loss and not protection against axonal degeneration. Neuronal cell bodies are not the targets of the claimed methods for treatment of PN. The neuronal cell body and the axon are biologically separate structures that respond differently to nervous system injury (Coleman, M., Axon degeneration mechanisms: commonality amid diversity. Nat Rev Neurosci, 2005. 6(11): p. 889-98) (Attached hereto as Exhibit D). Thus, upon information and belief, one of skill in the art would understand both that the therapeutic target of the claimed methods (axonal degeneration) is different than described by Saatman, and that any success in treatment of neuronal cell trauma does not predict that AK295 would be effective in treatment of axonal degeneration for peripheral neuropathy (PN).

10. With respect to the Wang reference, although the authors, including the co-inventor on the '360 application Dr. Jonathan Glass (see his declaration in Exhibit B), demonstrated the inhibitory effect of AK295 on axonomy and vincristine-induced axonal degeneration *in vitro*, it was still not obvious to those of skill in the art, including myself and Dr. Glass, that AK295 would provide effective inhibition in a whole animal model, even in view of the teachings of Saatman regarding the use of AK295 to treat mice with head trauma. First, evidence that a compound helps to treat one disorder (head trauma) does not lead to the conclusion that the compound will be useful to treat other disorders effected by different biological mechanisms (e.g., axonal degeneration associated with PN). Second, as understood by those of skill in the art, many compounds having *in vitro* activity do not have the same, if any, activity *in vivo*. Based upon this general knowledge and due to other factors and the skepticism of many of skill in the art (discussed in greater detail below) as to the *in vivo* activity of AK295 and its usefulness for treating axonal degeneration, we were doubtful of the potential success

with AK295 for the in vivo treatment of axonal degeneration and almost abandoned testing of the compound.

11. Wang describes an *in vitro*, cell based models of vincristine neurotoxicity, but in spite of this teaching, my co-inventor and I were unable to develop a whole animal model of vincristine-induced neuropathy in order to test the hypothesis that AK295 would be useful for treatment of PN. We had to experimentally examine other neurotoxic agents until we found one that allowed the testing of AK295 in an animal model of PN.

12. Dr. Ray Bartus, who has extensive experience in the field of neurological diseases and their treatment and with AK295 and other calpain inhibitors (see the Declaration of Dr. Ray Bartus, Exhibit C), previously investigated AK295 for the treatment of stroke. In a conversation with my co-inventor, Dr. Glass, Dr. Bartus expressed the opinion that our approach to protecting against axonal degeneration in PN by using AK295 "would not work" (See Exhibit C, paragraph 8). He expressed the belief that AK295 would not be orally active and that he did not think that it was possible to get AK295 into an animal in a therapeutically practical manner. This conversation almost prevented Dr. Glass and I from pursuing AK295 as a treatment for PN and conducting the animal experiments demonstrating that AK295 would be useful for treatment of PN.

13. Upon information and belief, no other investigators have pursued the use of AK295 for the treatment of PN in animals. AK295 has been available since 1994. Prior investigators thus had access to AK295, but were apparently unable to develop a method for treatment of PN based on the teachings of Saatman and Wang. Moreover, other calpain inhibitors such as calpastatin were readily available, and yet, upon information and belief, no one tried to use these to treat PN.

14. Peripheral neuropathies constitute a major category of neurological illness affecting millions of people worldwide. PN is a major dose-limiting complication of

commonly used anti-cancer agents, including the Vinca alkyloids (vincristine, vinblastine), platinum-based drugs (cisplatin, carboplatin, oxaliplatin) and the taxanes (paclitaxel and Taxotere). In the case of paclitaxel (Taxol), data presented on a Gynecological Oncology Group (GOG) study at ASCO 2002 suggested that greater efficacy could be achieved if more cumulative Taxol was administered. These data suggest that drugs that mitigate PN (e.g. calpain inhibitors) if used in combination with chemotherapy will likely result in heightened efficacy of anti-cancer regimens because patients will be less likely to discontinue or reduce the dose of anti-cancer agents because of the complication of PN. PN is the most frequent neurotoxic side effect of drugs used for a wide spectrum of human diseases. In addition, common diseases such as diabetes mellitus, HIV infection, auto-immune disorders, and cancer are also frequently complicated by the onset and progression of debilitating peripheral neuropathies. The most common peripheral neuropathy in industrialized nations is diabetic polyneuropathy that may be present in up to 66% of type 1 diabetic patients and in nearly 59% of type 2 diabetic patients. Based on the foregoing and upon information and belief, there is an urgent need for a treatment for PN.

15. Upon information and belief, no treatments currently exist that prevent or repair the axonal degeneration that causes PN. The clinical management of axonal degeneration neuropathies is inadequate and is restricted to palliation of pain with analgesics and physical and occupational therapy for management of disability. No intervention, other than the removal of an offending toxic agent, has yet to demonstrate a significant therapeutic effect in axonal peripheral neuropathies. Other companies have tried to develop treatments for Peripheral Neuropathy, but they have thus far failed. A similar lack of success has been experienced in the fields of diabetic neuropathy and HIV neuropathy.

Conclusion

16. Based on the foregoing and upon information and belief, and further in view of the skepticism of experts in the field, the long-felt need in the art, and the general lack of alternative technologies, I submit that the claimed methods of treating axonal degeneration *in vivo* with AK295 or the other claimed compounds would not have been obvious to one of skill in the art knowledgeable of the combined teachings of Saatman and Wang.

17. Furthermore, upon information and belief, I submit that based solely on the teachings of Saatman and Wang, it would have taken extensive experimentation, with little likelihood of success, for one of skill in the art to achieve the claimed methods of the '360 application.

DECLARATION

I hereby declare that all statements made herein are of my own knowledge are true and that all statements are made on information and belief and are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

James C. Powers
James C. Powers, Ph.D.

Dec. 15, 2006
Date